7598/linuron CR

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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Review of Linuron Reproduction Study.
Identifying Number 352-326 and Action Code 800.

TO: Ingrid Sunzenauer, Review Manager
Special Review Branch (TS-767C)

and

Robert Taylor, PM #25
Registration Division (TS-767C)

FROM: Charles N. Aldous, Ph.D.
Section V, Toxicology Branch/HED (TS-769C)
Charles N Aldous April 22, 1985

THRU: Laurence D. Chitlik, DABT
Section Head, Section V
Toxicology Branch/HED (TS-769C)
LDC 4/22/85

and

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch/HED (TS-769C)
4/23/85

ACTION REQUESTED: Review of Linuron rat reproduction study under Accession # 255829.

RECOMMENDATIONS: This study is classified as Core Supplementary Data. A major deficiency with this study is the lack of gross and histopathology data on adults. This information is important because reproductive effects observed in the study cannot otherwise be interpreted in light of parental effects.

Several items of information in addition to the above concern are requested in the RECOMMENDATIONS section on page 3 of the review which follows. These are:

1. Clarification of the dates and durations of dosing, and times of sacrifice.

2. Any data which relates to reproduction effects of linuron should be submitted as it is obtained. Of specific interest is information which might derive from cross-mating of F_{2B} parents, as proposed for an ancillary test in the protocol amendment of Oct. 1, 1984 (see p. 4, this review).

Excerpts of data submitted by du Pont on Linuron were included in this review. (12 pages). These pages may be requested by writing Freedom of Information (A-101), EPA, Washington, D.C. 20460. Requesters will be asked to sign an Affirmation of Non-multinational Status.

For excerpts, see D-75998.

1. CHEMICAL: Linuron
3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea
(Lorox®, INZ-326)
Tox. Chem. No. 528

2. TEST MATERIAL: Linuron, Tech. (94.5% purity). Lot T80311-81.
Haskell sample identification No. 14,703

3. STUDY/ACTION TYPE: Reproduction, rat.

4. STUDY IDENTIFICATION: Multigeneration reproduction study in rats with 3-(3,4-dichlorophenyl)-1-methoxy-1-methylurea (Lorox®, Linuron, INZ-326).

Medical Research Project No. 4580-001
Haskell Laboratory Report No. 436-84
Issue date: October 26, 1984
Study Director: Timothy P. Pastoor, Ph.D.
Sponsor: E. I. du Pont de Nemours and Company
EPA Accession #255829

5. CONCLUSIONS AND DISCUSSION: The dosing regime was as follows: Three successive parental generations (F_0, F_{1B}, and F_{2B}) of rats were fed dietary levels of 25, 125, or 625 ppm linuron in their diets from the time that they weighed about 100 g for approximately 90-day periods prior to matings for respective first litters. Dosing continued through mating (males) or weaning (females) of respective second generations.

Females of all three generations had lower body weights than controls by the end of respective 90-day pre-mating feeding periods in the 625 and 125 ppm groups (Table 1). Male body weights were not affected at the 125 ppm level, but were reduced at 625 ppm. Tendencies toward reduced food consumption and reduced food efficiency among 625 ppm adults (Tables 2A and 2B) give further evidence of an effect at this dose. This indicates an LEL of 125 ppm and a NOEL of 25 ppm for systemic effects. At the 625 ppm level, body weight gains were significantly lower for both sexes during respective 90-day pre-mating periods (Table 2). Alopecia was observed for both sexes in the F_0 and F_{1B} parental animals at 625 ppm (Table 3). No histopathological examinations were performed on parental animals, hence not all required information pertinent to toxicity in adults was available.

Several reproductive parameters were significantly affected in the 625 ppm groups. Fertility was appreciably reduced in generations F_{2A}-F_{3A} (Table 4). Pup survival was consistently lower in 625 ppm rats (see Table 5). Many of the pup deaths occurred during the first 24 hours post partum (24 hour survival was reduced significantly in all but the F_{2B} generation, non-significant reductions in the F_{2B} litters). There was a trend (probably a treatment effect, but not statistically significant) toward decreased viability of 625 ppm pups from days 1-4.

Several effects on pups were observed with concomitant decrements in maternal health, largely manifest in reduced maternal weights. Although pup deaths after day 4 were uniformly uncommon in all dosage groups, weights of 625 ppm pups were, in most instances, significantly lower than controls from day 1 through weaning. At this dose, absolute liver and kidney weights of weanlings of both sexes were reduced. Histopathology of F_{2B} weanlings found frequent incidence of liver atrophy (decreased cytoplasmic clear spaces of hepatocytes, see Table 6 of this review).

Neonatal growth effects were concomitantly observed with maternal weight gain decrements down to the 125 ppm level. Weanling weights of 125 ppm animals were significantly ($p < 0.05$) lower than controls in F_{1B} males and in F_{2A} males and females (Table 5). Also, F_{2B} males and females were found to weigh somewhat less than respective controls (not significant at $p < 0.05$). Because of significant differences in some generations' mean litter weights and a consistent trend in other generations at the 125 ppm level, this reviewer concludes that there is a dose-related effect on pup weights at weaning, which extends down to the 125 ppm level. The most frequent instances of reduced weanling weights at the 125 ppm level related to offspring of F_{1B} dams (see Table 5), which dams had significantly lower weights at weaning times of the F_{2A} and F_{2B} litters than did other dams at comparable times (Table 1). Thus the reproductive LEL was 125 ppm and the NOEL was 25 ppm.

This study is classified as Core Supplementary Data. The reviewer found no inconsistencies of consequence within the data. The investigators' conclusions followed logically from the data. A major problem with the study is the lack of histological information on parental animals. Data as generated by the protocol amendment dated Oct. 1, 1984 (see p. 4, this review) was not included in the study. Possibly such data, if histology were included, could result in an upgrade of this study. Histological

data is necessary for studies such as the present one, in which marked infertility is observed. Major deficiencies of this study are summarized as follows:

A. Significant decrements in fertility and neonatal survivability were observed in high-dose groups, especially in the latter generations. Nevertheless, no evaluation was made of possible causes of infertility. In particular, there was no histopathology performed on any generation of parental animals.

B. There were no gross pathology data available for animals which died on study.

6. RECOMMENDATIONS: An upgrade of the present study is possible if histopathology data on adults can be provided. This is important because of marked reproductive effects of unknown etiology observed at the 625 ppm level. If reproductive organ specimens are not available from the present study, a supplementary study which reports examinations of tissues of comparably treated adults would be satisfactory.

The registrant should submit dates on which dosing of individual animals began, a clear indication of the duration of such dosing, and dates of sacrifices. This information is necessary because of the confusion which has been caused by ambiguities in the descriptions of the dosing regimen.

Data obtained by cross-breeding of F_{2B} parents or any other data obtained with respect to reproductive effects should be submitted as promptly as practicable.

7. BACKGROUND: The report alluded to two three-generation studies with two litters per generation, in which male and female rats were fed 0 or 125 ppm technical linuron. In the first study, F_{2B} and F_{3A} weanlings had depressed body weights compared to respective controls. Mean body weights of F_{3B} weanlings were increased compared to controls. The second study, identically designed, found no growth depression in F_{2B} or F_{3A} weanlings. Neither study found compound-related effects on reproduction parameters. Neither study was identified by unique study numbers, nor were raw data for those studies included in this report.

The high dose for the present study was established on the basis of an unidentified range-finding study, in which Crl:CD® rats were fed diets of 0, 125, 625, or 1250 ppm linuron for 4 weeks. In that study, decreased body weights were observed at 625 and 1250 ppm. This reviewer does not identify a need for detailed review of this subchronic study, although a hardcopy of these background data has apparently not been submitted for review, primarily because the rangefinding study did not assess mating performance as it was not a reproduction study.

A two-year rat feeding study was submitted (Kaplan, A.M. et al., 1980, MRID #s 29679 and 29680) which found several effects on reproductive organs in the course of histopathological examinations. Frequencies of testicular interstitial cell adenomas were significantly increased in a dose-related fashion in 125 and 625 ppm rats. Absolute testicular weights were significantly increased at these dose levels. The epididymedes of 125 and 625 ppm males had dose-related increases of perivasculitis and vasculitis. Females had increased incidence of endometrial cystic hyperplasia at the 625 ppm level. These animals were, of course, not dosed in utero as in a reproduction study.

Several addenda were made in the protocol over the course of the present study. The initial protocol, dated Nov. 19, 1982, called for a two-generation study. The study was to have involved 90-day feeding periods for the F_0 and F_{1B} parents, with two litters from each generation. Histopathology of selected F_{2B} weanlings was anticipated at that time. An amendment dated May 8, 1984 called for 20 male and 20 female weanlings from each group to be selected to generate F_{3A} and F_{3B} litters, with the provision that perhaps the F_{2B} parents would be cross-mated (i.e. controls with high-dose parents) at breeding time for the F_{3B} generation, if warranted by results from the F_{3A} litters. Finally, an amendment dated October 1, 1984 stated that the objectives of the study were met, and that the present study would be terminated with the F_{3A} generation. The plans for future studies were as follows (p. 138 of the report):

> "The F_{2B} parents will be retained, given their respective diets, and cross mated (control groups with high-dose groups) to produce "F_{3B}" litters. However, data from the cross-mating will not be used in the final report since the constraints of the experimental design (e.g. no true control group) do not meet the objectives of this study. The purpose of cross-mating these F_{2B} rats will be for preliminary investigation only. The fate of F_{2B} rats will be for investigations other than those specifically stated in the protocol or protocol amendments."

MATERIALS AND METHODS: (by study author)

The methods section of the investigators' report is appended to this review.

COMMENTS ON METHODS:

The dosing portion of the protocol is not clearly stated in the report. This reviewer contacted Dr. Timothy P. Pastoor, the Research Toxicologist who supervised this study, and learned that the study involved continuous feeding of test material of parental (F_0 - F_{2B}) males (through matings for respective second litters) and females (through weanings of second litters). This dosing regime is consistent with the methods information given on pp. 13 and 21. References which describe discrete 90-day dosing periods (i.e. pp. 22, 23, 24, 26, 117, 120, 121, 122, 123, and 124) should be interpreted as dosing which was performed prior to first matings, but which dosing continued through the times of mating or

weaning of respective second litters; regardless of the fact that most of these pages appear to suggest that dosing ended after the 90-day dosing periods.

Subsequent generations were not started on linuron diets immediately at weaning: it can be seen from Tables 37-45 of the report that weights at weaning were 40-50 g, however body weights of the three generations at initiation of respective 90 day feeding periods were usually over 100 g.

The methods section states on p. 26 that "F_0, F_{1B}, and F_{2B} rats which died during the feeding phases were necropsied and examined for the presence of disease. Following completion of the examination, the carcasses and tissues of the rats were discarded." Dr. Pastoor confirmed in a recent telephone conversation that these examinations were performed. No pathology data were given in the report for the 14 rats which died on study, although the identities of these animals were given on pp. 31-32.

The methods section did not call for any gross pathological or histopathological data to be gathered for any adult animals which were sacrificed on schedule. Therefore there was no provision to assess probable causes of infertility for matings which were not successful. The lack of any histological examinations of adults in this study was confirmed by Dr. Pastoor by telephone on April 8, 1985.

The way in which individual litter data were presented made the reviewing somewhat awkward. Individual litter data tables in the appendices did not list and identify animals which were infertile or which died prior to delivery. It was thus difficult to reconcile this information with the "Reproduction and Lactation Indices" tables.

The following data were gathered on pups:

1. Numbers of pups at birth (or as soon as possible after birth), at 24 hr, at 4 days, 12 days, and 21 days (weaning).

2. Litter weights at 24 hr and 4 days. Reduced litter weights after culling litters to a maximum of 10 pups were recorded in F_{2A}, F_{2B}, and F_{3A} generations only.

3. Individual weights of fetuses at 21 days, recorded by sex under individual litters.

The disposition of pups was as follows:

1. "F_{1A}, F_{2A}, and F_{3A} weanlings were sacrificed and discarded without pathological examination."

2. "F_{1B} and F_{2B} weanlings were selected for the 90-day feeding phases (and matings for the next generation) on the basis of being, by general observation, representative of the general health of all pups in the litter". The selection was therefore not random.

3. "Pups found dead before weaning were discarded without pathological examination."

4. Ten males and ten females were selected from the control and high dose F_{2B} weanlings for gross and histopathological examination.

RESULTS:

Test material was stable at room temperature for at least 10 days when mixed with the feed. Test material was well distributed in the mixed feed, and levels measured by HPLC assay were within a few percent of nominal levels.

There was no treatment-related mortality in any generation of the study.

Body weight gains were significantly reduced for adults in the 625 ppm groups of all generations (Table 2, abstracted from Tables 4, 5, 15, 16, 26, and 27 of the investigators' report). Body weight gains of 125 ppm females of the F_0 and F_{2B} generations were also reduced. Mean body weights of the F_0, F_{1B} and F_{2B} females of the 125 ppm groups were significantly lower than controls, partly because of lower weights at onset of dosing in the latter 2 generations (Table 1, abstracted from Tables 3, 14, 25, and 37-45). Male body weights and body weight gains were unaffected by 125 ppm linuron.

Table 1.
Weights in grams of females in respective parental generations in linuron reproduction study

Generation	Time of weighing	Dosage Group (ppm) 0	25	125	625
F_0	Day 0 of test	116	116	114	116
	Day 91 of test	260	272[a]	240[a]	231[a]
	Weaning of F_{1A} litter	308	318	306	271[a]
	Weaning of F_{1B} litter	335	336	322[?]	294[a]
F_{1B}	Day 0 of test	111	101	99[a]	82[a]
	Day 91 of test	267	270	247[a]	224[a]
	Weaning of F_{2A} litter	305	295	285[a]	260[a]
	Weaning of F_{2B} litter	334	338	319[a]	271[a]
F_{2B}	Day 0 of test	128	134	123	95[a]
	Day 91 of test	291	287	260[a]	226[a]
	Weaning of F_{3A} litter	300	311	303	255[a]

[a]Significant, $p < 0.05$
[?]Not marked in Table 3 of report as significant, however probability given as 0.03.

Table 2. Mean body weight gains in grams of rats fed 0, 25, 125, or 625 ppm Linuron for 90 days

	CONCENTRATION (ppm)	0	25	125	625
	DAYS ON TEST				
F_0 Males	0 - 28	200	196	190	144*
	28 - 56	100	103	69*	100
	56 - 84	63	70	77*	33*
	0 - 91	372	380	345	288*
F_0 Females	0 - 28	81	88	74	62*
	28 - 56	38	40	18*	40
	56 - 84	24	23	30	10*
	0 - 91	144	156*	125*	115*
F_{1B} Males	0 - 28	204	216*	199	164*
	28 - 56	120	130	117	100*
	56 - 83	58	65*	59	47*
	0 - 91	400	430*	395	327*
F_{1B} Females	0 - 28	85	92*	84	82
	28 - 56	39	44	36	38
	56 - 83	22	24	21	18*
	0 - 91	156	169*	146	142*
F_{2B} Males	0 - 28	195	189	191	152*
	28 - 56	120	119	118	95*
	56 - 84	80	68*	75	59*
	0 - 98	403	386	389	319*
F_{2B} Females	0 - 28	73	70	64	68
	28 - 56	47	40	43	36
	56 - 84	36	28	24*	22*
	0 - 98	163	152	137*	130*

*Significant, $p < 0.05$.

Food consumption was modestly reduced in 625 ppm males of the F_0 and F_{2B} generations and in F_0 females during the 90-day pre-breeding feeding periods (see Table 2A, from Tables 6-29 of the report: statistical significance not assessed). A modest trend toward lower food efficiency was evident in 625 ppm males and females in all generations (Table 2B, from Tables 8-31 of the report).

Table 2A
Mean Daily Dietary Consumption of Rats Fed for 90 Days With Diets That Contained Linuron

Sex	Generation	Days on Test	Dietary Concentration (ppm) 0	25	125	625
Male	F_0	0-28	23.4	23.7	23.0	20.3
		28-56	25.0	25.0	22.9	22.2
		56-84	24.5	26.0	24.9	21.9
		0-91	24.3	25.0	23.6	21.5
	F_{1B}	0-28	23.8	24.2	22.6	20.5
		28-56	27.5	29.4	26.9	25.4
		56-83	26.6	28.5	26.4	25.8
		0-91	25.9	27.4	25.4	23.9
	F_{2B}	0-28	27.0	27.0	26.5	23.0
		28-56	27.8	27.6	27.2	24.1
		56-84	30.5	29.3	30.3	25.3
		0-98	28.2	27.7	27.6	23.8
Female	F_0	0-28	17.0	16.8	15.6	15.2
		28-56	17.5	18.0	15.5	15.4
		56-84	16.9	16.5	17.1	15.1
		0-91	17.1	17.1	16.1	15.3
	F_{1B}	0-28	16.6	16.6	15.6	14.9
		28-56	17.8	17.8	17.2	17.4
		56-83	17.9	17.7	17.3	18.3
		0-91	17.5	17.4	16.7	17.0
	F_{2B}	0-28	19.0	19.3	17.8	18.9
		28-56	20.6	20.8	19.0	21.2
		56-84	18.8	18.6	17.0	18.6
		0-98	19.4	19.4	17.5	19.1

Table 2B.
Mean Food Efficiency of Rats Fed for 90 Days
With Diets That Contained 0 to 625 ppm Linuron

Sex	Generation	Days on Test	Mean Food Efficiency (g weight gain/g diet consumed) 0	25	125	625
Male	F_0	0-28	.304	.295	.294	.254
		28-56	.143	.147	.108	.161
		56-84	.092	.096	.111	.054
		0-91	.168	.167	.160	.147
	F_{1B}	0-28	.307	.319	.315	.287
		28-56	.156	.158	.155	.141
		56-83	.081	.084	.083	.068
		0-91	.169	.172	.171	.150
	F_{2B}	0-28	.258	.250	.257	.237
		28-56	.154	.155	.155	.141
		56-84	.093	.083	.088	.083
		0-98	.146	.142	.144	.137
Female	F_0	0-28	.170	.187	.171	.146
		28-56	.077	.079	.041	.092
		56-84	.050	.049	.062	.023
		0-91	.093	.100	.086	.083
	F_{1B}	0-28	.182	.199	.193	.196
		28-56	.079	.089	.075	.078
		56-83	.046	.049	.044	.035
		0-91	.098	.107	.096	.092
	F_{2B}	0-28	.137	.131	.128	.128
		28-56	.081	.069	.081	.061
		56-84	.068	.054	.051	.041
		0-98	.085	.080	.080	.070

The only clinical effect which appeared to be treatment-related was alopecia. Table 3, abstracted from Tables 12, 23, and 34 of the investigators' report, illustrates the alopecia incidence in parental animals. The F_{2B} animals did not show as clear a response as the previous two generations.

Table 3. Incidence of alopecia in rats fed linuron for 13-14 weeks.[a]

Dietary Concentration (ppm)	0	25	125	625
Generation/Sex				
F_0/Male	0	0	0	6 (4)
F_0/Female	1 (8)	0	1 (13)	8 (5)
F_{1B}/Male	0	0	1 (13)	3 (3)
F_{1B}/Female	1 (10)	0	2 (4)	5 (8)
F_{2B}/Male	0	1 (14)	2 (13)	1 (7)
F_{2B}/Female	4 (10)	2 (10)	5 (7)	7 (6)

[a]Median time-on-test when alopecia was first observed in parenthesis (weeks). Twenty rats per sex per test group at beginning of dosing periods.

A marked decrement in fertility was observed in the F_{2A} through F_{3A} litters of high dose animals (Table 4, from Tables 36-45 of the report).

The gestation index was 100% for all generations and doses, as all litters had at least one live pup. In the F_{1A} and F_{3A} high dose groups there were significant decreases in the percentages of pups born alive per litter. This was not a consistent finding across generations, as the F_{2A} and F_{2B} litters of 625 ppm animals had 97-99% live births.

In all cases, the high dose animals had appreciable postnatal losses (see Table 5). Decrements in viability from days 0-4 were statistically significant in all but the F_{2B} litters among the 625 ppm group. Most of these deaths were in the first 24 hours. Pup deaths from days 1-4 appeared to be high among 625 ppm groups from the F_{2A} generation onward. These values were not statistically significant, however they did indicate a meaningful trend.

Table 4

Summary of Reproduction and Lactation Parameters in Rats Fed Diets Containing 0, 25, 125, or 625 ppm Linuron

Reproduction/ Lactation Parameter	Dose (ppm)	Treatment Group Affected F_{1A}	F_{1B}	F_{2A}	F_{2B}	F_{3A}
Indices						
Fertility	0	90.0	85.0	100	95	89.5
%	25	90.0	85.0	95	75	85
	125	100.0	100.0	89.5	89.5	90
	625	100.0	89.5	63.2[a]	61.1[a]	52.6[a]
Gestation	0	100	100	100	100	100
%	25	100	100	100	100	100
	125	100	100	100	100	100
	625	100	100	100	100	100
Lactaction	0	100	100	100	100	86.3
Index, %	25	100	93.5	100	100	100
per litter	125	100	100	99.4	98.2	99.4
	625	100	100	100	95.6[a]	100
% Born	0	99.6	99.5	94.3	100	92.1
Alive	25	100.0	97.0	100	99	98.6
per litter	125	96.8	100	98.5	98.5[a]	98.1
	625	94.3[a]	92.7	97.4	99.2	74.8[a]
0-4 Day	0	97.9	100	93.9	98.6	92.1
Percent	25	98.9	93.4[a]	99.2	99.5	98.7
Viability	125	98.4	98.1	98.1	99.1	98.6
per litter	625	86.8[a]	92.0[a]	74.6[a]	86.8	58.8[a]
1-4 Day	0	98.7	100	99.6	99.7	98.8
Percent	25	100.0	96.5	99.2	100	99.6
Viability	125	99.5	98.5	100	99.1	100
per litter	625	98.7	98.5	87.8	87.7	85.9
Litter	0	100	100	95	100	82.4
Survival,	25	100	94.1	100	100	100
(percent)	125	100	100	100	100	100
at weaning	625	100	94.1	91.7	90	70.0[a]

[a]Significant, $p < 0.05$

It can be seen from the Table 5 that pups which survived to day 4 generally survived to weaning, regardless of treatment group. Pup weights at 24 hours were generally low in the 625 ppm groups, and the high dose animals remained behind controls in pup weights through the weaning period, despite the significantly smaller litter sizes of the high dose group, even after culling (Table 5). There was also an apparent trend for intermediate dose pups to gain less weight than controls or 25 ppm pups between days 4 and 21. This was significant at $p < 0.05$ for F_{1B} males and F_{2A} pups of both sexes. Additionally, F_{2B} weanlings of both sexes weighed somewhat less than controls (not significantly different at the $p < 0.05$ level).

Table 5

Summary of Reproduction and Lactation Parameters in Rats Fed Diets Containing 0, 25, 125, or 625 ppm Linuron

Reproduction/ Lactation Parameter	Dose (ppm)	Treatment Group Affected F_{1A}	F_{1B}	F_{2A}	F_{2B}	F_{3A}
Mean post-partum pup counts per litter						
Day 4, after reduction	0	9.7	9.8	9.2	9.8	9.4
	25	9.8 (101)[b]	9.4 (96)	9.8 (107)	9.8 (100)	9.7 (103)
	125	9.6 (99)	9.6 (98)	9.9 (108)	9.5 (97)	9.5 (101)
	625	7.8[a] (80)	7.8[a] (80)	6.7[a] (73)	6.9[a] (70)	4.2[a] (45)
Day 12	0	9.7	9.8	9.2	9.8	9.4
	25	9.8 (101)	9.2 (94)	9.8 (107)	9.8 (100)	9.7 (103)
	125	9.6 (99)	9.6 (98)	9.8 (107)	9.5 (97)	9.5 (101)
	625	7.8[a] (80)	7.8[a] (80)	6.7[a] (73)	6.7[a] (70)	4.2[a] (45)
Day 21 (weaning)	0	9.7	9.8	9.2	9.8	8.1
	25	9.8 (101)	9.2 (94)	9.8 (107)	9.8 (100)	9.7 (120)
	125	9.6 (99)	9.6 (98)	9.8 (107)	9.4 (96)	9.4 (116)
	625	7.8[a] (80)	7.8[a] (80)	6.7[a] (73)	6.7[a] (68)	4.2[a] (52)
Mean pup Weights						
24 hours both sexes	0	6.6	6.6	7.1	6.5	6.8
	25	6.5	6.0	7.0	6.5	6.7
	125	6.8	6.6	6.7[a]	6.5	6.8
	625	5.7[a]	6.2	5.8[a]	6.1	6.0[a]
Day 4, both sexes before litter reduction	0	9.9	9.7	10.7	9.7	9.8
	25	9.6	8.8	10.5	9.8	9.8
	125	9.9	9.5	9.9[a]	9.5	9.9
	625	8.0[a]	8.6[a]	8.5[a]	8.4[a]	8.3[a]
Males at weaning	0	50.7	50.5	51.4	49.7	43.2
	25	50.2	49.6	48.8[a]	49.5	44.0
	125	48.9	46.8[a]	46.4[a]	47.9	40.4
	625	37.0[a]	40.1[a]	34.1[a]	38.5[a]	38.3
Females at weaning	0	47.9	47.7	49.4	47.8	41.8
	25	47.7	46.5	46.3[a]	47.6	42.3
	125	47.2	45.1	44.2[a]	45.4	40.8
	625	35.3[a]	38.2[a]	33.1[a]	37.0[a]	36.8[a]

[a]Significant, $p < 0.05$

[b]Percentage of corresponding control litter size.

Evaluation of F_{2B} weanlings at sacrifice found significant and apparently compound related effects only in the 625 ppm group. Final body weights and absolute liver and kidney weights of pups were reduced significantly in both sexes (Tables 47 and 49 of the investigators' report). Weights of livers relative to body weight were decreased significantly in males and appeared to be lower in females (not statistically significant) of the 625 ppm group. Kidney relative weights were unchanged. Except for increased relative weights of brains in both sexes at the 625 ppm level (absolute weights unchanged), no other significant changes in organ weights were recorded.

No compound-related effects were observed during gross pathological examination of F_{2B} weanlings (the only group necropsied). The only compound-related histopathology evident in F_{2B} weanlings was in the liver. Both sexes were affected, but only at the high dose (see Table 6 of this review, abstracted from Tables V and VI of the appendix, on pages 342-347 of the report). The text of the pathology report, found on pp. 307-308 of the investigators' report, summarized by stating "The changes were atrophy and decreased cytoplasmic clear spaces of hepatocytes".

Table 6. Incidence of histopathologic findings in F_{2B} weanlings in rat reproduction study using linuron.

Sex / Tissue/Lesion	Lesion Grades[a] (1,2,3,P,0)	Dose Levels (ppm) 0	25	125	625
Male					
Liver		10[b]	10	10	10
Atrophy, hepatocytes		1[c](-,1,-,-,-)	-	2(1,1,-,-,-)	8 (2,3,3,-,-)
"Cytoplasmic vesiculation, decreased, hepatocytes"[d]		1(-,1,-,-,-)	-	2(1,1,-,-,-)	10 (2,6,2,-,-)
Female					
Liver		10	10	10	10
Atrophy, hepatocytes		2(-,-,2,-,-)	1(-,-,1,-,-)	2(-,2,-,-,-)	10(1,3,6,-,-)
"Cytoplasmic vesiculation, decreased, hepatocytes"		2(-,-,2,-,-)	1(-,-,1,-,-)	2(-,2,-,-,-)	10(1,3,6,-,-)

[a]Lesion grades: 1= Slight change; 2= Moderate change; 3= Marked change; P= Change present, severity not graded; - = Change not present or tissue within normal histologic limits.

[b]Number of tissues examined per group (livers of 10 animals examined in all cases).

[c]Incidence of lesions observed per group, followed by breakdown of lesion grades in parenthesis.

[d]The text reads "decreased cytoplasmic clear spaces of hepatocytes".

Tox Chem No. 528 Linuron File Last Updated _____ Current Date 12 Apr 85

Study/Lab/Study #/Date	Material	EPA Accession No.	Results: LD_{50}, LC_{50}, PIS, NOEL, LEL	TOX Category	CORE Grade/ Doc. No.
3-Generation reproduction - rat; Haskell Lab; #436-84; 10/26/84	Tech. 94.5% pure	Accession #255829	Reproductive NOEL = 25 ppm Reproductive LEL = 125 ppm (lower weanling weights). Pup weights more consistently reduced at 625 ppm (days 1-21). Liver and kidney weights reduced at 625 ppm. Liver atrophy at 625 ppm. Also, lower fertility, reduced pup survival on days 0-4 in 625 ppm groups. Systemic NOEL (adults) = 25 ppm Systemic LEL (adults) = 125 ppm (Reduced weights and weight gains of dams prior to mating, reduced dam weights at weaning). Reduced body weight gains of both sexes, and alopecia at 625 ppm. Levels tested: 25, 125, and 625 ppm.		Supplementary